Use of Minute-by-Minute Cardiovascular Measurements during Tilt Tests to Strengthen Inference on the Effect of Long-Duration Space Flight on Orthostatic Hypotension

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Typical methodology for evaluating the effects of spaceflight on orthostatic hypotension (OH) has been survival analysis of tolerance times from 80° head-up tilt tests. However when scheduled test durations are short, there may not be enough failures to allow survival analysis to adequately estimate and compare the effects of flight phase (e.g. pre-flight, number of days post-flight), flight duration, and their interaction, as well as interactions with effects of interventions or countermeasures. The problem is exacerbated in the presence of a repeated measures design, in which subjects participate in tilt tests during various flight phases. Here we show how it is possible to dramatically improve the efficiency of statistical inference in this setting by making use of the additional information contained in minute-by-minute observations of cardiovascular parameters thought to be reflective of progression towards presyncope during tilt testing. **Methods:** We retrospectively examined operational tilt test (OTT; 10-min 80° head-up tilt) data from 20 International Space Station (ISS) and 66 Shuttle astronauts 10 d before launch (L-10), on landing day (R+0) and during recovery (R+1, R+3, R+6-10) depending on the level of participation. Data from 5 ISS astronauts tested on R+0 or R+1 who used non-standard countermeasures were excluded. In addition to OTT survival time, 8 cardiovascular parameters (CP: heart rate, systolic, diastolic, and mean arterial blood pressure, pulse pressure, stroke volume, cardiac output, and total peripheral resistance) that might be predictive of progression towards presyncope were measured every minute of each OTT. Statistical analysis was predicated on a two-stage model of causation. In the first stage, flight duration and time from landing affect the astronauts' degree of OH, which is manifested in the time trends and variation of the above CPs during OTTs. In the second stage, the behavior of these parameters directly affects OTT survival time. Actual analysis proceeded in the opposite direction. First we identified those CPs or linear combinations that best predicted OTT survival regardless of what spaceflight conditions led to OTT completion or presyncope. From these, we calculated a summary statistic (one per OTT) that best predicted survival. We then used mixed-model regression analysis to relate changes in the summary statistic to flight phase and duration. Inference on the effects of phase, duration, and their interaction on OH follows directly from this second analysis. **Results**: A linear combination (W) of diastolic blood pressure (DBP) and stroke volume (SV) was found to be the best predictor of OTT survival using the complete data set of minute-by-minute observations of CPs for each OTT. Furthermore, the log-transformed standard deviation of W ($Z = \log S_W$) was found to be a strong predictor of survival in the reduced data set consisting of one observation per OTT. In other words, this measure of variability of W during an OTT was the best indicator of whether or not the subject could complete the 10-min test, with higher variability (i.e. higher values of Z) being associated with greater probability of failure. In the mixed-model regression analysis where Z was now treated as a outcome with flight phase and duration groups (ISS and STS) as predictors, we found that there was a significantly more variability in W (higher values of Z) for both groups at R+0, but with no evidence of an interaction until R+3, when the ISS group still had inflated variability, but not the STS group. **Conclusions**: Variability of the cardiovascular index W recovers more slowly after long- compared to short-duration spaceflight. Since high variability of W has also been shown to be predictive of OTT failure, a primary manifestation of OH, a logical conclusion is that recovery from OH also is slower after long-duration compared to short-duration spaceflights.